Rejection under 35 USC §112

Claims 7, and 10 to 14 are rejected under 35 USC §112, first paragraph as containing subject matter which was not described in the specification. Applicants respectfully traverse this rejection.

Claim 7, it should be noted, is an original filed claim. Claim 10, from which is now depends is only narrower in scope than originally filed claim 1. Therefore, claims 7 and 10 to 14 should meet all the necessary requirement of conveying to the skilled artisan the what the meets and bounds of the claim scope are. The specification, at the time of filing, is believed to have provided sufficient guidance to the skilled artisan on the relevant process steps necessary to make and use the invention. The dechlorination via hydrolysis is not a new process step. It existed in the prior art at the time of filing of the application, and as such it is not necessary that it be incorporated into a Claim –8 like statement. The specification provides details to be found in EP 141927 and EP 302644. Basis for dechlorinating via hydrolysis to give X is hydroxy is found in EP141927 page 6, line 16 to page 7, line 2 (the page 5, line 17 reference is the citation in the granted patent).

The statement is :

"The compound of formula (A) or a salt thereof may be prepared by converting the group X in a compound of formula (III) ... ... to an -OH group by means of hydrolysis preferably acid hydrolysis".

Claim 19 as correctly noted by the Examiner should claim the novel intermediate of claim 5, and has been amended accordingly. The Examiner's attention to this is greatly appreciated.

In view of the remarks, reconsideration and withdrawal of the rejection to the claims under §112, 1rst paragraph is respectfully requested.

Rejection under 35 USC §102 (b)

Claims 5 and 15 to 19 are rejected under 35 USC §102(b) as being anticipated by EP 302,644. Applicants respectfully traverse this rejection.

EPO 302644 ('644) generically discloses a process to make a compound of Formula (A). This disclosed "generic" process is actually two different processes as the compound of Formula (II) can react with either a compound of Formula (III), a 5,7-dioxaspiro[2.5]octane-4,8-dione, or it can react with a compound of Formula (V)

to eventually produce a compound of Formula (A), the desired end product. The reaction process which uses a compound of Formula (V) is generally referred to herein as the "bromotriester route".

The '644 application does not, generically or specifically, disclose the specific combination of reaction steps claimed herein. In order to be an anticipation it must teach the combination of steps, in the same order, as claimed herein.

The process steps on pages 5 and 6 of the '644 reference do not teach when the starting material, 2-aminochloropurine (ACP) is to be dechlorinated. The only guidance in the '644 application is the specific examples directed to use of Formula (V) compounds which produce the final compound, Famciclovir. This bromotriester route discloses the following sequence of reactions, which are shown in detail in Annex 1 of the previously submitted Geen Declaration.

In short, those steps are:

a) coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate (formula (V)) to 2-amino-6-chloropurine (formula (II)) (Description 11);
b) removal of the 6-chloro substituent (R_2) (Description 12);
c) decarboxylation (Example 3);
d) reduction (Step A(b)); and
e) *O-acetylation* (Step A(c)).

However, in order to dechlorinate the tricarboxylate intermediate in Description 12, the compound is first isolated. This isolation, due to the process conditions used, and the additional impurities produced by this process, etc., requires 7 additional steps, which are also described in detail in paragraphs 3 and 4 of the Geen declaration.

In contrast, the present process, as described in Annex 3 of the Geen declaration, does not require these isolation steps, and further does not produce 2 of the additional impurities of the '644 process. See paragraphs 4 and 6 of the Geen declaration.

The present invention requires the following steps:

a) coupling of compound of formula (V) with a compound of formula (II) to yield a compound of Formula (VI) (Example 1);
b) decarboxylation (Example 1) (to give Compound 5, Annex 3);
c) reduction (Example 2);
d) *O*-acetylation (Example 2); and
e) removal of the 6-chloro substituent (R_2) (Example 3).

In Applicants process the 6-chloro substituent remains in place until the final step of the synthesis instead of being removed after the coupling step (a) in '644.

Thus, EP0 302644 does not specifically disclose the presently claimed process. The reference must provide a certain degree of precision with respect to the specific compounds claimed. Applying these holdings to this process, the reference does not clearly and unequivocally direct the skilled artisan to retain the chlorine in the intermediates used therein to improve the yields, reduce process steps and improve reaction conditions for large commercial scale production. Therefore, the '644 reference does not provide the precision necessary for anticipation under §102.

The Examiner has stated that a signed copy of the Geen Declaration has not been received at the USPTO. The matter is being looked into further to ascertain the status of the signed copy. If it can not be found, a newly signed declaration will be submitted.

In light of this reconsideration and withdrawal of the rejection to the claims under 35 USC §102(b) is respectfully requested.

Rejection under 35 USC § 103

Claims 1 to 7, and 10 to 15 are rejected by the Examiner under 35 USC §103(a) as being unpatentable over EP 302,644 ('644) Applicant also respectfully traverses this rejection.

The bromotriester route, as described above and disclosed in EPO 302644, is a process which has been found to be inconvenient for use on a large, commercial scale. A primary reason for such inconvenience is because it requires a chromatography separation of the N-7 and N-9 isomers resulting from the addition/coupling reaction, Description 11 (page 15) of the '644 application. The present process was developed as an improvement in the bromotriester route in order to facilitate large scale commercialization of the process.

The teachings of the EPO 302644 reference would not lead the skilled artisan to carry out the sequence of steps as presently claimed herein, i.e. coupling, decarboxylation, reduction and esterification, followed finally by removal of the 6-chloro substituent.

The unexpected results achieved by retention of the 6-chloro throughout the claimed process is significant.

The previously submitted declaration by Dr. Graham Geen demonstrated that the bromotriester process described in '644 produces an overall yield of about 11%, whereas the instant process produces an overall yield of about 41%. The significant improvement in overall yield comes from not one step which benefits from the 6-chloro retention but from two different process steps.

These particularly advantageous and unexpected features of the present invention are not taught nor suggested in the '644 application. The skilled artisan would not be motivated by the '644 reference to retain the chlorine in the chemical intermediates. A skilled artisan would not be directed to the improved benefits of yield in the decarboxylation step, nor to the improved yields in the reduction and acetylation steps.

The Examiner has however, states that these unexpected effects are unpersuasive for the reasons enunciated in paper #4.

In view of this, Applicant submits a declaration which compares the two processes, that claimed herein wherein the chlorine is removed at the end versus the '644 process wherein the chlorine is removed earlier (after the coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate to 2-amino-6-chloropurine).

The results will show that the overall yield of the instant process is 41% of a crystalline solid, representing a 41% yield of usable famciclovir, i.e. famciclovir of a pharmaceutically acceptable quality, which is in comparison to an overall yield of 14% of a crude brown oil representing a 0% yield of usable famciclovir from the '644 process.

These data clearly indicate that the continued presence of the 6-chloro substituent during decarboxylation and through to the final step of the process is responsible for the advantages of the instant process over that process as described in the '644 patent.

This data should clarify the comments of the Examiner regarding particular reaction conditions employed, etc., such as removal of the column chromatography steps or the nature of the ester obtained following decarboxylation of the compound of formula (VI).

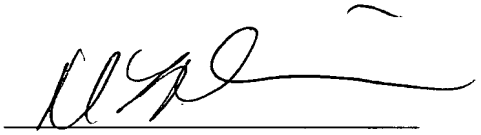
As the declaration is being signed in England, it will be forwarded under separate cover, however a copy of the Annex is attached herewith for the Examiner's convenience.

In light of these remarks and claim amendments, reconsideration and withdrawal of the rejection to the claims under 35 USC §103 is respectfully requested.

Conclusion

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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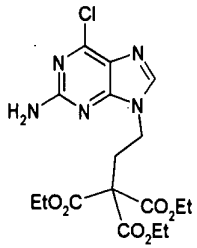
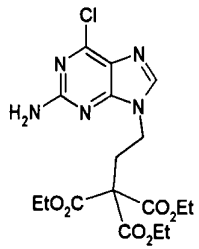
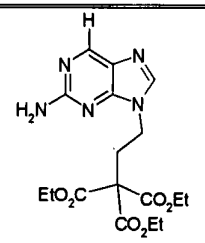
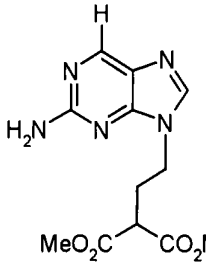
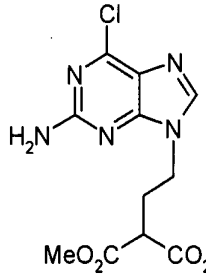
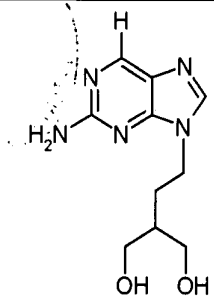
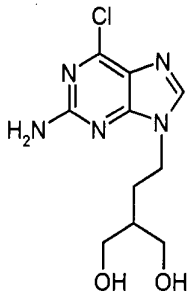
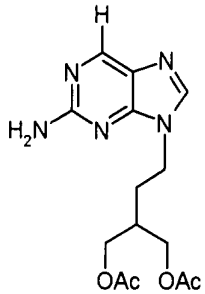
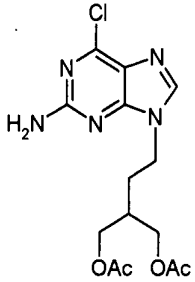
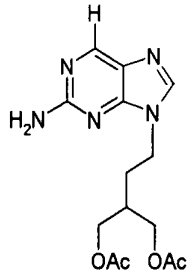
ANNEX

	"EP 302644 Process"			US 09/265,926		
Stage Number	Product	Comments		Product	Comments	
Stage 1 Step 1		Yield	32.23 g (%)		Yield	Not given
		Form	Red/brown oil		Form	Red oil
Step 2		Yield	17.87 g (%)	Not Applicable		
		Form	Viscous oil			
Step 3		Yield	14.79 g (%)		Yield	12.0 g (65%
		Form	Yellow oily solid.		Form	Crystalline solid
		N9 and N7 were not separated Purity Approx 45% by NMR			Assay 95%, selective crystallisation of N9 isomer	

Stage 2						
Step 1		Yield	21.06 g		Yield	Quantitative wet cake
		Form	Yellow oily solid		Form	Wet cake
		Evaporated to dryness. No purification by precipitation/washing possible.			Cake washed with water to remove impurities	
Step 2		Yield	8.31 g		Yield	70%
		Form	Brown oil		Form	Crystalline solid
		Famciclovir as a crude brown oil. Purity Approx. 30% by NMR.			Product of high purity (98%) and utilisable form for a pharmaceutical intermediate	
Step 3	Not Applicable				Yield	90%
					Form	Crystalline solid
					Famciclovir of pharmaceutical acceptable quality	
Overall Yield	0% (usable famciclovir) (weight yield 14%)			41% (usable famciclovir)		
Form	Crude Oil			Crystalline solid		